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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KAM, CHIH MIN	
ART UNIT	PAPER NUMBER
1656	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,682	SHI ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 11-15* is/are rejected.

7)☒ Claim(s) *10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Staphylokinase (SAK) as the elected thrombolytic protein, hirudin as the elected anticoagulant protein, and IEGR as the elected linker peptide in the response to restriction requirement filed April 3, 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). In the supplemental amendment filed April 3, 2009, claims 8, 9 and 11 have been amended. Upon reconsideration, the species election is withdrawn. Therefore, claims 1-15 and all the sequences are examined.

Informalities

The disclosure is objected to because of the following informalities:

2. The specification recites amino acid sequences such as IEGR, GSIEGR, PRIEGR, GSGPR and GSLGPR at pages 3, 4 and 7-8 without providing sequence identifiers "SEQ ID NO:". These sequences are not listed in the Sequence Listing. Applicant must comply with the requirements of sequence rules (37 CFR 1.821-1.825) to include all the sequences in the sequence listing. Appropriate correction is required.

Objection to New Matter Added to Specification

3. The supplemental amendment filed April 3, 2009 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: a linker peptide recognized by a blood coagulation factor refers to tetrapeptide of LGPR (originally cited as tripeptide of GPR) or

peptide containing LGPR or LGPL (originally cited as GPR) (paragraphs [0011], [0021], [0024]).

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Objections

4. Claims 7-11 are objected to because the claim recites amino acid sequences such as IEGR, LGPR, GSIEGR, PRIEGR, GSLGPR and LGRP without providing a sequence identifier "SEQ ID NO:". Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 13-14 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 8, 9 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 8, 9 and 11 are directed to a fusion protein comprising a thrombolytic protein, an anticoagulant protein and a linker peptide, where the linker peptide is an amino acid sequence LGPR, which can be recognized by coagulation factor FIIa (thrombin), or a peptide containing LGPR; a fusion protein such as SAK-GSLGPR-HV2 of staphylokinase and hirudin linked by linker peptide GSLGPR; and a method of preparing a fusion protein comprising a thrombolytic protein and an anticoagulation protein, wherein the method comprises linking the thrombolytic protein gene and the anticoagulant protein gene together via a sequence encoding IEGR or LGRP-containg peptide.

The "original" specification indicates the term "linker peptide recognized by blood coagulation factor" refers to the tetrapeptide of IEGR, peptide containing IEGR sequence, tripeptide of GPR or peptide containing GPR (page 4, lines 14-16), and a fusion protein of SAK-GSGPR-HV2 composed of staphylokinase and hirudin linked by linker peptide GSGPR (page 4, lines 25-26), although Example 3 indicates preparation of fusion protein of STH (SAK-GSLGPR-HV2; pages 7-8). It is known in the art that the thrombin cleavage site is Phe/Gly-Pro-Arg (for example, see Rezaie *et al.,* U.S. Patent 5,298,599, column 6, lines 27-33). Since the linker peptide is based on the cleavage site recognized by factor Xa or thrombin, thus it is reasonable to indicate the tetrapeptide of IEGR and the tripeptide of GPR as the linker peptide. However, the amended specification recite the tetrapeptide of LGPR as the linker peptide (paragraphs [0011], [0021] and [0024]). The lack of description on the tetrapeptide of LGPR or

LGRP (claim 11) as the cleavage site recognized by thrombin, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

7. Claims 1-8 and 11-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-8 and 11-15 are directed to a fusion protein comprising a thrombolytic protein, an anticoagulant protein and a linker peptide, wherein the thrombolytic protein can be staphylokinase (SAK), tissue-type plasmingoen activator (t-PA), streptokinase (SK) , urokinase (UK), urokinase-like plasminogen activator (u-PA), venom and mutants thereof that activates other hemolytic factors or have thrombolytic activity, wherein the anticoagulant protein can be hirudin, antithrombin III, venom and mutants thereof, and wherein the linker peptide is a peptide recognized by blood coagulation factor; a method of preparing the fusion protein; a pharmaceutical composition comprising a fusion protein; the use of a linker peptide in the preparation of a fusion protein; and a method of treating a disease associated with thrombosis by administering a fusion protein.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other

materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The specification indicates a fusion protein comprising a thrombolytic protein, an anticoagulant protein and a linker peptide, wherein the thrombolytic protein refers to the proteins having thrombolytic activity, e.g., staphylokinase (SAK), tissue-type plasmingoen activator (t-PA), streptokinase (SK), urokinase (UK), urokinase-like plasminogen activator (u-PA), venom and mutants thereof that activates other hemolytic factors or have thrombolytic activity, wherein the anticoagulant protein refers to proteins having anticoagulant activity, e.g., hirudin, antithrombin III, venom and mutants thereof, and wherein the linker peptide is a peptide recognized by blood coagulation factor; (page 4). However, the specification does not describe any venom or mutant of a thrombolytic protein or an anticoagulant protein. While the specification provides specific examples of fusion proteins of SAK-GSIEGR-HV2 and SAK-GSLGPR-HV2 (Examples 1 and 2), the specification does not provide sufficient description for a genus of variants of the fusion proteins comprising various thrombolytic proteins, anticoagulant

proteins and linker peptides when there is substantial variation in the whole genus of fusion proteins. Since there is no structure-activity correlation for variants of thrombolytic proteins and anticoagulant proteins (e.g., venom or mutants thereof), a skilled artisan cannot predict the structures of functional thrombolytic proteins and anticoagulant proteins. The lack of description on the structure-activity correlation for the variants of thrombolytic protein and anticoagulant protein and lack of representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 2, 4 and 13-14 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claims 2 and 4 are indefinite because of the use of the term "venom and mutants thereof". The term cited renders the claim indefinite, it is not clear what the term means with respect to the thrombolytic protein and the anticoagulant protein, and what structures the venom or mutants of the proteins have.

10. Claims 13-14 provide for the use of a linker peptide in the preparation of a fusion protein, but, since the claim does not set forth any steps involved in the method/process, it is unclear

what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-7 and 11-14 are rejected under 35 U.S.C. 102(b) as being anticipated by van Zyl *et al.* (Thrombosis Research 88, 419-426 (1997)).

van Zyl *et al.* teach the production of recombinant antithrombotic and fibrinolytic protein, PLATSAK in *E. coli*, wherein the PLATSAK gene comprises staphylokinase, fused via a cleavable linker by FXa to an antithrombotic peptide of 29 amino acids comprising RGD sequence, a part of fibrinopeptide A and the tail of hirudin, and wherein the purified protein has antithrombin activity, antiplatelet activity and fibrinolytic activity (Abstract; Figs. 1 and 2; page 422; claims 1-7 and 11-14).

12. Claims 1, 2, 4-7 and 11-15 rejected under 35 U.S.C. 102(b) as being anticipated by Dawson *et al.* (U.S. Patent 5,434,073, published on 7/18/1995).

Dawson *et al.* teach the production of fusion proteins by linking together fibrinolytic (e.g., streptokinase) and/or anti-thrombotic protein (e.g., hirudin) with a cleavable linker (factor Xa (IEGR) or thrombin cleavage site (X-PR)), their preparation, pharmaceutical compositions comprising the fusion proteins and their use in the treatment of thrombotic diseases (column 1, lines 11-16; columns 2-5; claims 1, 2, 4-7 and 11-15), e.g., construction of a vector for the

expression of hirudin-IEGR-streptokinase fusion gene (Examples 8, 9) and expression of streptokinase-IEGR-hirudin fusion gene and hirudin-IEGR-streptokinase (Examples 14-15).

13. Claims 12 and 15 rejected under 35 U.S.C. 102(b) as being anticipated by Potter *et al.* (U.S. Patent 6,015,787, published on 1/18/2000).

Potter *et al.* teach the use of a fusion protein comprising a calpastatin peptide and a signal peptide capable of delivering the fusion protein into a cell, where the fusion protein can be prepared as a therapeutic composition and can be used in reduction of coronary thrombosis in coronary bypass surgery, reduction of thrombosis and other thrombosis associated diseases (column 1, line 38-column 2, line 6; column 5, line 59-column 6, line 56; Example 7; claims 12 and 15). Since the claims do not recite the structure of the fusion protein, any fusion protein that is in a pharmaceutical composition or that treats thrombosis would meet the criteria of the claims.

Claim objections

14. Claim 10 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

15. Claims 1-9 and 11-15 are rejected; and claim 10 is objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Chih-Min Kam/
Primary Examiner, Art Unit 1656

CMK
May 8, 2009